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Guidance for Industry

Cell-Based Products for Animal Use

DRAFT GUIDANCE

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Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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Additional copies of this draft guidance document may be requested from the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at either http://www.fda.gov/AnimalVeterinary/default.htm or http://www.regulations.gov.

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Guidance for Industry

Cell-Based Products for Animal Use

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM, we) is aware that many potential veterinary therapies may be produced using cell-based products. Developers of such products for veterinary use have approached CVM for clarification regarding the regulation of these products. This draft guidance for industry (GFI) describes CVM's current thinking on cell-based products for animal use that meet the definition of a "new animal drug."

This draft guidance is for firms and individuals developing cell-based products, including "animal stem cell-based products" (ASCPs). CVM encourages developers of cell-based products to contact the Center early in product development.

FDA's guidance documents, including this draft guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency's guidances means that something is suggested or recommended, but not required.

II. PURPOSE AND SCOPE

This draft guidance is intended to:

- Clarify FDA's position that it has jurisdiction over cell-based products meeting the definition of new animal drug
- Clarify FDA's current thinking on how existing regulations apply to ASCPs
- Establish a common vocabulary for ASCPs
- Establish a risk-based category structure for ASCPs
- Encourage industry to communicate and interact with CVM early in product development

Cell-based products meeting the definition of a new animal drug are subject to the same statutory and regulatory requirements as other new animal drugs. Although this draft guidance focuses on ASCPs meeting the definition of a new animal drug, it also applies to other cell-based products.

Cell-based products may incorporate, or be the product of, genetic engineering (GE) technologies, including recombinant DNA (rDNA) constructs. Cell-based products that contain rDNA constructs can result in the production of genetically engineered animals. If you intend to produce genetically engineered cell-based products, or animals produced from them, there will likely be additional risk-based questions regarding your product. [1] You should contact CVM for more information early in product development if you are producing, or intend to produce, genetically engineered cell-based products or animals produced from them.

III. WHAT IS AN ANIMAL STEM CELL-BASED PRODUCT (ASCP)?

In this draft guidance, the following terms apply:

- The term "cell-based products" means those articles containing, consisting of, or derived from cells that are intended for implantation, transplantation, infusion, or transfer into an animal recipient. In this draft guidance, the term "cell-based products" refers to those products meeting the definition of a new animal drug.

- The term "animal stem cell-based products" (ASCPs) means articles containing, consisting of, or derived from stem cells for use in animals. ASCPs are subset of cell-based products containing, consisting of, or derived from cells such as stem cells, progenitor cells, precursor cells, stem cell-like cells, reprogrammed cells, and other cell types with similar properties. In this draft guidance, the term ASCP refers to those products meeting the definition of a new animal drug.

- The term "stem cell" means a non-terminally differentiated, self-renewing cell that harbors the ability to produce mature, differentiated daughter cells. Stem cells serve to regulate or participate in normal tissue homeostasis and embryonic and fetal development.

Generally, cell-based products, including ASCPs, meet the definition of a new animal drug if, among other things, those products are intended to diagnose, cure, mitigate, treat, or prevent disease in animals, or are intended to affect the structure or function of the animal, and do not meet any statutory exemptions.

IV. STATUTORY AUTHORITY

The following sections of the Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 321 et seq.) establish FDA's authority over new animal drugs:

- Section 201(g) (21 U.S.C. 321(g)) defines a drug, in part, as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals;" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals."

[1] As an example, see Guidance for Industry 187, "Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs." Guidance for Industry 187 pertains to genetically engineered animals containing heritable rDNA constructs; however, much of this guidance may also be relevant to non-heritable rDNA constructs.

- Section 201(v) (21 U.S.C. 321(v)) defines a "new animal drug," in part, as any drug intended for use for animals that is not generally recognized as safe and effective for use under the conditions prescribed, recommended, or suggested in the drug's labeling.
- Section 512(a), (21 U.S.C. 321(a)) states the conditions that render a drug "unsafe." This section states, in part, that a new animal drug is "deemed unsafe" for a particular use unless the use of the drug is approved, conditionally approved or indexed.
- Section 512(j) (21 U.S.C. 321(j)) provides for an exemption from the requirements in section 512(a) for products used solely for investigational use. 21 CFR part 511 describes the responsibilities and obligations of sponsors qualifying for legal investigational use.

Cell-based products, including ASCPs, that are intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease or are intended to affect the structure or function of the animal generally meet the definition of a new animal drug, and are regulated as new animal drugs. These cell-based products require an approved or conditionally approved new animal drug application or index listing in order to be legally marketed. Investigational use of cell-based products used solely for research purposes is allowed, provided the requirements set forth in 21 CFR part 511 are met.

CVM encourages firms and individuals developing cell-based products, to visit the Center's website at http://www.fda.gov/AnimalVeterinary/default.htm to learn more about the pathways to legal manufacture and distribution of new animal drugs. Firms and individuals developing, marketing, or distributing cell-based products should contact CVM with questions regarding new animal drug applications and approval requirements.

V. CATEGORIES OF ASCPs

ASCPs may be collected, derived, harvested, or isolated from any embryonic, fetal, post-natal somatic, or reproductive tissue. ASCPs may be classified according to the relationship between the cell donor and ASCP recipient. The source of the cells, the relationship between donor and recipient, the manufacturing process and the intended use of the cells can affect safety, effectiveness, or quality of the ASCP. For the purposes of this guidance, CVM divides ASCPs into the following categories:

A. Xenogeneic

Xenogeneic ASCPs are those in which the cells are collected from a donor animal of one species and used in a recipient animal of a different species.

B. Allogeneic

Allogeneic ASCPs are those in which the cells are collected from a donor animal and used in a recipient animal of the same species, but the donor and recipient animals are not the same individual.

C. Autologous

Autologous ASCPs are those in which the cells are collected from, and the ASCP is administered to, the same animal (the donor and recipient are the same individual animal). CVM further divides this category into the following two types:

1. Type I

Autologous ASCPs are Type I products if they meet any of the following criteria:

a. The ASCP is more than minimally manipulated (see definition below).
b. The ASCP is for non-homologous use (see definition below).
c. The ASCP is for use in a food-producing animal.
d. The ASCP's effect is dependent on the metabolic activity of its living cells.
e. The manufacture of the ASCP involves the combination of the cells with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent unless the addition of the agent raises new safety concerns with respect to the product.
f. The finished ASCP is combined with or modified by the addition of a component that is another drug or device.[2]

In this draft guidance, the following terms apply:

- The term "more than minimal manipulation" means processing that alters the relevant biological characteristics of cells or tissues. Examples of more than minimal manipulation include, but are not limited to, cell expansion, directed cell differentiation, and addition of purified trophic factors.

- The term "homologous use" means the repair, reconstruction, replacement or supplementation of a recipient's cells or tissues with a cell-based product that performs the same basic function or functions in the recipient as in the donor (for example, cartilage derived cells intended to replace damaged cartilage in the recipient). For the purposes of this document, homologous use refers to the intended function of the ASCP in the recipient. Any product not meeting this definition is considered to be for a non-homologous use.

[2] The term "device" is defined in section 201(h) of the FD&C Act.

2. **Type II**

Autologous ASCPs are Type II products if they meet *all* of the following criteria:

a. The ASCP is minimally manipulated.
b. The ASCP is for homologous use.
c. The ASCP is for use in non-food producing animals.
d. The manufacture of the ASCP does not involve the combination of the cells with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new safety concerns with respect to the product.
e. The finished ASCP is not combined with or modified by the addition of any component that is a drug or device.

In this draft guidance, the term "minimal manipulation" means processing that does not alter the relevant biological characteristics of cells or tissues. Examples of minimal manipulation include, but are not limited to, centrifugation and cryopreservation.

You should contact CVM's Office of New Animal Drug Evaluation (ONADE) to discuss where your ASCP fits within these categories.

VI. PREAPPROVAL REQUIREMENTS

A. Xenogeneic, Allogeneic, and Autologous Type I ASCPs

1. New Animal Drug Application

Xenogeneic, allogeneic, and autologous Type I ASCPs require premarket review to be legally marketed. At this time, FDA believes that a New Animal Drug Application (NADA) will be the most appropriate pathway for legally marketing most ASCPs.[3] The requirements for NADAs are described in 21 C.F.R. part 514. The requirements for approval of an NADA include, for example, a demonstration of safety, effectiveness, and manufacturing quality.[4]

Due to the nature of ASCPs, the information provided to meet the requirements for approval of an NADA for an ASCP may differ from traditional drug products. CVM evaluates ASCPs using a risk-based approach that examines the risks and benefits to the treated animal, as well as the

[3] Indexing and conditional approval are also pathways to legal marketing of products under certain specified circumstances involving minor species and minor uses in major species; however, FDA believes that at this time the indexing and conditional approval requirements may be difficult to meet for most ASCPs due to the novel nature of the products, the inter-related nature of safety, effectiveness, and manufacturing, and the current state of the science.
[4] Safety includes target animal safety, human user safety, human food safety, and safety to other animals and humans in contact with the recipient animal. The requirements for approval of an NADA also include evaluation of the labeling and all other information pertinent to the product. In addition, as required by the National Environmental Policy Act, FDA assesses the impact an approval decision may have on the environment.

likelihood of harm to other populations that may be affected by the treated animal (for example, transmission of communicable disease that may spread beyond the recipient animal). CVM's evaluation is conducted on a case-by-case basis because the potential hazards and risks are likely to be unique to each ASCP. General considerations for evaluating the safety, effectiveness and manufacturing quality of ASCPs are described below.

a. Safety and Effectiveness

Preapproval safety assessments of ASCPs should address the risks of the individual product. In addition to standard safety testing, other safety evaluations depend on the specific characteristics of the product and may include, but are not limited to, evaluation of the following:

- Tumorigenicity
- Immunogenicity
- Donor selection criteria
- Transmission of adventitious agents
- Long term-safety
- Cell survival
- Biodistribution
- Ectopic tissue formation

Preapproval effectiveness evaluations must demonstrate substantial evidence of effectiveness.[5] Adequate and well-controlled studies are required to demonstrate that the ASCP has its intended effect.[6]

We recommend that you contact CVM early in your development process to discuss what types of evidence will be required to demonstrate the safety and effectiveness of your product.

b. Chemistry, Manufacturing, and Controls

In the Chemistry, Manufacturing, and Controls (CMC) technical section you must include information regarding the production and manufacture of ASCPs.[7]

Controlled practices and procedures should be employed in the manufacture of the ASCP to ensure that tissue handling and cellular isolation are reliable, consistent, preserve cellular function and integrity, and prevent contamination of the product.[8] All finished new animal drug products,

[5] 21 U.S.C. 360b(d)(1)(E); 21 CFR 514.4
[6] 21 U.S.C. 360b(d)(3); 21 CFR 514.117
[7] 21 U.S.C. 360b(b)(1); 21 U.S.C. 360b(d)(1)(C)
[8] The current Good Tissue Practices (GTPs) in 21 CFR 1271 apply to human cellular and tissue based products. While these regulations only apply to human products, the principles described in GTPs may provide a basic reference for the handling of cells and tissues used in the manufacture of ASCPs.

including ASCPs, are required to meet current Good Manufacturing Practices (cGMPs).[9]

We recommend that you contact CVM early in your development process to discuss how to provide data and information to support the CMC technical section of your NADA.

2. Investigational Use

The requirements for investigational use of new animal drugs are provided in 21 CFR 511. There are two categories of investigational exemptions; one for tests *in vitro* and in laboratory research animals and one for clinical investigations.

If you intend to investigate ASCPs in client-owned animals you should contact CVM for information on how to establish an Investigational New Animal Drug (INAD) file prior to conducting clinical investigations. The "investigational exemption" provided for in 21 CFR 511 allows sponsors to ship or deliver the product for use in client-owned animals.

a. Investigational use *in vitro* and in laboratory research animals

New animal drug products, including ASCPs, intended solely for *in vitro* studies or tests in laboratory research animals used solely for research purposes may be eligible for an "investigational exemption" under 21 CFR 511.1(a). This regulation allows a sponsor to deliver the product for investigational use *in vitro* and in laboratory research animals, provided that it is labeled as described in the regulation.

b. Clinical investigations (e.g., use in client-owned animals)

New animal drug products, including ASCPs, used in clinical investigations (e.g., studies in client-owned animals) may be eligible for an investigational exemption under 21 CFR 511.1(b). This exemption allows a sponsor to legally deliver the product for investigational use in clinical studies if the sponsor meets certain conditions. These conditions include using the product only for bona fide scientific investigations, submission of notices of claimed investigational exemption (drug delivery notices) to FDA, retaining all reports received from investigators, providing for current monitoring of investigations, and use of the labeling statements provided in the regulation.[10] Sponsors must also report any findings that may suggest significant safety hazards to FDA and all investigators.[11] These conditions also prohibit

[9] For the purposes of this document, Good Manufacturing Practice regulations refers to 21 CFR part 210, Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs and 21 CFR part 211, Current Good Manufacturing Practices for Finished Pharmaceuticals.
[10] 21 CFR 511.1(d)(2), 21 CFR 511.1(b)(4), 21 CFR 511.1(b)(8)(i), 21 CFR 511.1(b)(8)(ii), 21 CFR 511.1(b)(1)
[11] 21 CFR 511.1(b)(8)(ii)

commercial distribution and test marketing, unduly prolonging distribution, or representing that the product is safe and effective.[12] For a complete list of requirements refer to §§511.1(b) and 511.1(d)(2)).

CVM encourages sponsors of investigational new animal drugs to establish an investigational new animal drug (INAD) file prior to beginning clinical investigations in client-owned animals. In order to meet the requirements for an investigational exemption, sponsors must submit a notice of claimed investigational exemption (NCIE) to CVM prior to clinical investigations in client-owned animals.[13] If a sponsor has not previously contacted CVM to request an INAD, CVM will establish one upon receipt of an NCIE.[14]

B. Autologous Type II (ATII) ASCPs for Non-Food Producing Animals

Although ATII ASCPs require an approved NADA, conditional approval or index listing to be legally marketed, FDA recognizes that these products pose a lower risk to human and animal safety than other categories of ASCPs when used in non-food producing animals and are, therefore, a lower enforcement priority. However, firms marketing such products should be aware that the agency may take enforcement action against them at any time when the agency concludes it is necessary to further the purposes of the FD&C Act.

FDA expects all ASCPs to comply with the manufacturing standards and post-marketing responsibilities listed below:

- The finished ASCP is required to meet current Good Manufacturing Practices (cGMPs) in 21 CFR parts 210 and 211. Controlled practices and procedures should be employed in the manufacture of the ASCP to ensure that tissue handling and cellular isolation are reliable, consistent, preserve cellular function and integrity and prevent contamination of the product.[15] We recommend that you contact CVM with questions regarding appropriate manufacturing standards.
- All ASCP manufacturing facilities must register with the agency and drug list their products prior to marketing (21 CFR 207). (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/DrugRegistrationandListing/ucm078801.htm)

[12] 21 CFR 511.1(b)(8)(iii)-(v)
[13] 21 CFR 511.1(b)(1)(4)
[14] Under the Animal Drug User Fee Act of 2003 (ADUFA), user fees are assessed at the time the INAD file is established unless the sponsor qualifies for a fee waiver. For guidance on these user fees and how to request waivers and reductions from these fees, see GFI # 170 "Animal Drug User Fees and Fee Waivers and Reductions" and GFI # 173 "Animal Drug Sponsor Fees under the Animal Drug User Fee Act (ADUFA)".

[15] The current Good Tissue Practices (GTPs) in 21 CFR 1271 apply to human cellular and tissue based products. While these regulations only apply to human products, the principles described in GTPs may provide a basic reference for the handling of cells and tissues used in the manufacture of ASCPs.

- All labeling and promotion must be truthful and not misleading (21 USC 352(a) and 21 USC 321(n)).
- Manufacturers of ATII ASCPs should report adverse events to FDA. (http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/AnimalDrugForms/ucm048817.pdf)

C. ASCPs for use in Food-Producing Animals

FDA expects manufacturers of all ASCPs meeting the definition of a new animal drug and intended for use in food-producing animals to obtain approval for these products. In addition, FDA reminds sponsors that they must comply with 21 CFR part 511 for investigational use of their ASCP.

New animal drug products, including ASCPs, intended for use in food-producing animals have the potential to affect edible tissues entering the human food supply. As with any investigational use of a new animal drug in food-producing animals, edible products of investigational animals are not to be used for food unless authorization has been granted by FDA (21 CFR 511.1(b)(5), 21 CFR 511.1 (b)(4)(v)(a)).

VII. POST-APPROVAL RESPONSIBILITIES

Post-approval responsibilities for ASCPs as set forth in the applicable regulations include, but are not limited to, the following:

- All ASCP manufacturing facilities must register with the agency and drug list their products prior to marketing (21 CFR 207). (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/DrugRegistrationandListing/ucm078801.htm)

- All labeling and promotion must be truthful and not misleading (21 U.S.C. 352(a) and 21 U.S.C. 321(n)). The labeling associated with an ASCP may only prescribe, recommend, or suggest use under the conditions approved in the labeling that was submitted as part of the approval (21 U.S.C. 360b(a)(1)). This labeling must use the same language and emphasis as in the approval, including descriptions of relevant hazards and precautions (21 CFR 201.105(d)).

- Adverse events must be reported to FDA (21 CFR 514). (http://www.fda.gov/AnimalVeterinary/SafetyHealth/ReportaProblem/ucm212682.htm)

- Complete records must be kept of all information relevant to the safety and effectiveness of the ASCP that has not been previously submitted to FDA (21 CFR 514.80(a)(1)).

- Sponsors must submit drug experience reports to CVM containing reports of data, studies and other information related to experience with the ASCP (21 CFR 514.80(a)(2).

- Sponsors must submit to CVM information on all proposed changes or changes that have been made to the ASCP (21 CFR 514.8(b)). The nature and timing of the reporting may be different depending on the risk that could be introduced by the change. We recommend that you contact CVM regarding any post-approval changes to your product prior to filing.

- Sponsors must submit supplemental applications for changes affecting the safety or effectiveness of a product. These supplements require approval by CVM prior to marketing (21 U.S.C. 360(e)(1)(F)).

VIII. DEFINITIONS

The following are definitions for terms used in this draft guidance document.

Adventitious Agent: Foreign agents that have been unintentionally introduced into the manufacturing process of a product. Examples of adventitious agents include, but are not limited to, bacteria, viruses, fungi, mycoplasmas, rickettsia, protozoa, parasites, and prions.

Allogeneic Use: The implantation, transplantation, infusion, or transfer of cells from a donor animal into a recipient animal of the same species where the donor and recipient animals are not the same individual.

Animal Stem Cell-Based Products (ASCPs): Articles containing, consisting of, or derived from stem cells for use in animals. ASCPs include cell-based products containing, consisting of, or derived from cells such as stem cells, progenitor cells, precursor cells, stem cell-like cells, reprogrammed cells, and other cell types with similar properties.

Autologous Use: The implantation, transplantation, infusion, or transfer of cells back into the individual animal from which the cells were recovered.

Cell-Based Products: Articles containing, consisting of, or derived from cells that are intended for implantation, transplantation, infusion, or transfer into an animal recipient.

Combined Cell-Based Product: A cell-based product that is combined with or modified by the addition of any component that is a drug or device **or** a cell-based product where the manufacture of the product involves the combination of the cells with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent.

Differentiation: The developmental process occurring when a cell or tissue increases its level of organization or complexity and acquires a more specialized function.

Homologous Use: The repair, reconstruction, replacement or supplementation of a recipient's cells or tissues with a cell-based product that performs the same basic function or functions in the recipient as in the donor. For the purposes of this document, homologous use refers to the function of the cells in the cell-based product. Any product not meeting this definition for homologous use is considered to be for a non-homologous use.

Minimal Manipulation: Processing that does not alter the relevant biological characteristics of cells or tissues. Examples of minimal manipulation include, but are not limited to, centrifugation and cryopreservation.

More Than Minimal Manipulation: Processing that alters the relevant biological characteristics of cells or tissues. Examples of more than minimal manipulation include, but are not limited to, cell expansion, directed cell differentiation, addition of purified trophic factors, and intentional manipulation of the DNA of the cell including the introduction of rDNA constructs.

Progenitor Cell: A progenitor cell is an early descendant of a stem cell that retains the ability to differentiate, but in general, has lost the ability to self-renew. A progenitor cell is "more differentiated" than a stem cell and often more limited than a stem cell in the kinds of cells it can become. In this draft guidance, ASCPs include progenitor cells.

Self-Renewal: The mechanism by which subsequent generations of daughter stem cells retain the molecular and phenotypic identity, a quality termed 'stemness', and the functional characteristics of the parent stem cell if appropriate conditions are present or provided.

Stem Cell: A non-terminally differentiated, self-renewing cell that has the ability to produce mature, differentiated daughter cells that are of similar type to all or some of the various cell types in the body of an organism. Stem cells serve to regulate or participate in normal tissue homeostasis and embryonic and fetal development.

Xenogeneic Use: The implantation, transplantation, infusion, or transfer of cells from a donor animal of one species into a recipient animal of a different species.